

REMARKS

I. Status of the Claims

Claims 14-76 and 93-110 are pending in the application, with claims 14, 27, 39, 51, 64, 93, 95 and 97 being independent claims. Amendment is sought to all independent claims (*i.e.* claims 14, 27, 39, 51, 64, 93, 95 and 97). These amendments merely make explicit that which is already implicit in the claims, and is further supported by the specification at, for example, page 28. In addition, claims 19, 30, 42, 55, and 68 have been amended to correct the spelling of “nutriceuticals” to “nutraceuticals.”

It is acknowledged that the foregoing amendments are submitted after final rejection of the claims. However, because the amendments do not introduce new matter, and they either place the application in condition for allowance or at least in better condition for appeal, entry thereof by the Examiner is respectfully requested.

II. Rejections Under 35 U.S.C. § 103

A. Summary of the Present Rejections

In the Final Office Action dated October 20, 2006, the PTO set forth the following rejections under 35 U.S.C. § 103(a) which Applicants summarize below:

- At pages 2-4, claims 14-38, 51-76, 93-104 and 107-110 are alleged to be obvious over U.S. Patent 5,565,188 to Wong *et al.* (“Wong”) in view of U.S. Patent 6,177,103 to Pace *et al.* (“Pace”).
- At pages 4-5, claims 39-50, 105 and 106 are alleged to be obvious over Wong in view of U.S. Patent 6,316,022 to Mantelle *et al.* (“Mantelle”) and U.S. Patent 5,938,017 to Wik (“Wik”).
- At page 5, claims 39-50, 105 and 106 are alleged to be obvious over Wong in view of Pace, Mantel, and Wik.

The Examiner found Applicants' arguments filed June 28, 2006, to be unpersuasive and reasserted the rejections made in the March 31, 2006, Office Action. Applicants respectfully traverse the rejections for at least the following reasons. As an initial matter, Applicants incorporate by reference herein the remarks made in response to the previous Office Action.

B. The legal requirements of obviousness

On page 7 of the Office Action, the Examiner cites to *In re Keller*, 642 F.2d 413 (CCPA 1981), stating that:

The test for obviousness is not whether features of a secondary reference may be bodily incorporated into the structure of the primary reference; nor is it that the claimed invention must be expressly taught in any one or all of the references. Rather the test is what the combined teachings of the references would have suggested to those of ordinary skill in the art.

Since *Keller* in 1981, the courts have further elaborated how one would know "what the combined teachings would have suggested to those of ordinary skill in the art." They have determined that, in proceedings before the U.S. Patent and Trademark Office, the examiner bears the burden of establishing a *prima facie* case of obviousness based upon the prior art. See *In re Piasecki*, 223 USPQ 785, 787-88 (Fed. Cir. 1984). The Examiner can satisfy this burden only by showing some *objective* teaching in the prior art or that knowledge generally available to one of ordinary skill in the art would lead that individual to combine the relevant teachings of the references in such a way as to produce the invention as claimed. See *In re Fine*, 5 USPQ2d 1596, 1598 (Fed. Cir. 1988). There is no basis for concluding that an invention would have been obvious solely because it is a combination of elements that were known in the art at the time the invention was made. See *Fromson v. Advance Offset Plate, Inc.*, 755 F.2d 1549, 1556 (Fed. Cir. 1995). Instead, what is needed is a reason, suggestion, or motivation in the prior art that would motivate one of ordinary skill to combine the cited references, and that would also suggest a reasonable likelihood of success in making or using the claimed invention as a result of that combination. See *In re Dow Chem. Co.*, 837 F.2d 469, 473 (Fed. Cir. 1988). In the present case, the Examiner's burden has not been satisfied.

The Examiner also cited to *In re Spada*, 911 F.2d 705 (Fed. Cir. 1990) for a discussion of inherency. Applicants note that *Spada* discusses only the situation of a single reference being used as prior art under 35 U.S.C. §§102/103, and not the combination of two or more references, as here. Applicants also note that inherency and obviousness are legally distinct concepts, such that there is no such thing as “inherent obviousness.” See *In re Spormann*, 150 USPQ 449, 452 (C.C.P.A. 1966). That which is inherent cannot be obvious, since inherent information “is not necessarily known . . . [and] Obviousness cannot be predicated on what is unknown.” *Id.* Since the present rejection is based on obviousness, any contention by the Examiner that is based on the possible presence of inherent knowledge in the art (either in the cited references or in the general knowledge of those of ordinary skill) must necessarily fail.

C. Rejection of Claims 14-38, 51-76, 93-104 and 107-110 over Wong in view of Pace

- 1. Wong does not teach or suggest the claimed invention, and in fact teaches away from the claimed invention**
 - a. Wong does not teach the use of cationic surface stabilizers for nanoparticulate active agents**

The Examiner accepts that Wong does not anticipate the claimed invention because Wong does not expressly teach cationic surface stabilizers for nanoparticulate active agents. Rather, Wong teaches cationic surfactants may be used during sterilization as cloud point modifiers (Column 10). Cloud point modifiers are not the same as surface stabilizers. Specifically, Wong teaches that the cloud point modifier is being used to prevent dissociation of the surface stabilizer *from* the nanoparticle during sterilization (Col. 10, lines 30-38), rather than teaching that the cloud point modifier becomes associated *with* the particle. At no point does Wong disclose that the cloud point modifiers become associated with the *particles*.

b. Wong does not disclose that cationic surface stabilizers impart bioadhesive properties to a composition

Wong discloses that *block copolymers* are useful as bioadhesives. However, Wong does not teach that cationic surface stabilizers result in a bioadhesive composition. Thus, Wong discloses both block copolymers and cationic surfactants, but discloses *only* that block copolymers possess a desirable bioadhesion property. As such, Wong implicitly *teaches away* from the use of cationic surface stabilizers as agents to affect bioadhesion.

Wong discloses that block copolymers are useful as bioadhesives and/or control release agents because of their tendency to gel. Cationic surfactants are not disclosed to have this gellation property and, accordingly, one of ordinary skill in the art would therefore consider that cationic surfactants are not bioadhesive. Therefore, for this additional reason, Wong *teaches away* from the use of cationic surface stabilizers to affect bioadhesion.

Gellation involves the interaction of molecules of a block copolymer. This interaction is not inherently limited to those molecules of block copolymer on the surface of the individual nanoparticle. Thus, gellation also causes groups of nanoparticles to agglomerate together. As such, the average effective particle size *in vivo* would be expected to increase and would therefore fall outside the particle size limitations recited in the present claims. Accordingly, one seeking to create stable bioadhesive nanoparticles with an effective size of less than 4000 nm would not seek to use the block copolymers disclosed in Wong.

Applicants also note that the present application (page 13, lines 24-32) distinguishes between bioadhesion mediated by the mechanical/physical interaction, in which there is a “physical interlocking or interpenetration between a bioadhesive entity and the receptor tissue” (lines 24-26) and *chemical* interaction. The first sort of interaction is typical of gel forming polymers while, as the specification notes, it is the “chemical form of bioadhesion which is primarily responsible for the bioadhesive properties of the nanoparticles described in the patent” (lines 31-32). Applicants bioadhesive nanoparticles are, therefore, distinct from those the Examiner asserts is disclosed by Wong.

c. Wong does not teach that the therapeutic can be liquid at room temperature

At page 4 of the Office Action the Examiner also relies on Wong for providing an additional element which is recited in claims 39-50, 105 and 106: that the therapeutic is liquid at or near room temperature. The Examiner states that:

Wong is silent as to the teaching that the therapeutic is liquid at room temperature. However, it is the position of the Examiner that the therapeutic taught by Wong would be liquid at room temperature, because Wong teaches the use of the same active agent, *e.g.* naproxen. A chemical composition and its properties are inseparable.

Applicants agree that Wong does not disclose a therapeutic being liquid at room temperature. By contrast, Applicants fail to see how the fact that because Wong discloses naproxen, it would follow that naproxen is liquid at room temperature. The Examiner does not provide any evidence that naproxen would melt at room temperature. The melting point of naproxen is approximately 154-158°C, which is well above room temperature (20-25°C) and even above the boiling point of water (100°C). Applicants also note that the species of naproxen is not recited in those claims that depend from claim 39.

2. Pace does not cure the defects of Wong

Pace discloses the addition of surfactants to a solution to prevent particle agglomeration or particle growth during the formation of nanoparticles. Pace does not disclose that such surfactants impart a bioadhesive property to the nanoparticles, and certainly cannot teach the addition of an amount sufficient to cause the nanoparticles to bioadhere. Thus, Pace does not disclose nanoparticles with a cationic surface stabilizer in an amount effective to cause the nanoparticles to adhere to a biological surface. Accordingly, Pace does not anticipate nor render obvious the claimed compositions. As Pace does not provide the elements missing from Wong, Pace cannot cure the defects of Wong, and so the combination of Pace and Wong do not render obvious the claimed compositions or methods.

Pace also completely fails to recognize that cationic surface stabilizers may promote bioadhesion and is, in fact, not even interested in bioadhesion. For this addition reason, Pace

does not cure the defects of Wong and so cannot render obvious the presently claimed methods.

D. Rejection of Claims 39-50, 105 and 106 over Wong in view of Mantelle and Wik

1. Mantelle and Wik do not cure the defects of Wong or Pace

Mantelle does not disclose bioadhesion, nanoparticulate active agent particles, or the use of cationic surface active agents for promoting bioadhesion. Mantelle does not disclose that any of the drug particles are adherent in any way. Wik is in a nonanalogous art, and is only relied upon by the Examiner for the water soluble property of nicotine. None of these anticipate or render obvious the claimed invention, either alone or in combination. As none of these references provide the elements missing from Wong or Pace (or the combination of Wong and Pace), they do not cure the defects of Wong and Pace. Accordingly, the combination of these four references does not render obvious the claimed compositions or methods. Applicants respectfully request that the Examiner reconsider and withdraw the present rejection.

2. There is no motivation to combine the references

The Examiner has not demonstrated why one of ordinary skill in the art would be motivated to combine the cited references in an effort to obtain the claimed invention. As noted above, the law requires some *objective* evidence for the motivation to combine. *See In re Fine*, 5 USPQ2d 1596,1598 (Fed. Cir. 1988); *Fromson v. Advance Offset Plate, Inc.*, 755 F.2d 1549, 1556 (Fed. Cir. 1995); *In re Dow Chem. Co.*, 837 F.2d 469, 473 (Fed. Cir. 1988). There is no reason, suggestion, or motivation in the prior art that would motivate one of ordinary skill to combine the cited references, and that would also suggest a reasonable likelihood of success in making or using the claimed invention as a result of that combination. Not only is such objective evidence or motivation lacking, but Wong, the primary reference, actually *teaches away* from the combination of the cationic surfactants disclosed by Pace being used for bioadhesion. In view of the lack of objective evidence for combination and the teaching away from a combination, the person of ordinary skill in the art would not be

motivated to combine the references with any reasonable expectation of success. For at least this additional reason, Applicants respectfully request that the Examiner reconsider and withdraw the present rejections.

CONCLUSION

In view of the foregoing amendments and remarks, Applicants respectfully submit that all of the pending claims are now in condition for allowance. An early notice to this effect is earnestly solicited. If there are any questions regarding the application, the Examiner is invited to contact the undersigned at the number below.

The Commissioner is hereby authorized to charge any additional fees which may be required regarding this application under 37 C.F.R. §§ 1.16-1.17, or credit any overpayment, to Deposit Account No. 19-0741. Should no proper payment be enclosed herewith, as by a check or credit card payment form being in the wrong amount, unsigned, post-dated, otherwise improper or informal or even entirely missing, the Commissioner is authorized to charge the unpaid amount to Deposit Account No. 19-0741. If any extensions of time are needed for timely acceptance of papers submitted herewith, Applicant hereby petitions for such extension under 37 C.F.R. §1.136 and authorizes payment of any such extensions fees to Deposit Account No. 19-0741.

Respectfully submitted,

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